

REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1, 3, 5, 7, 8, 55-61 presently appear in this application, with claim 61 newly added, and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claim 54 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is obviated by the cancellation of claim 54 without prejudice.

Claims 1, 3, 5, 7, 8 and 54-60 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Gearhart et al., US Patent No. 6,562,619, in view of Zhang et al. (*Nat Biotechnol.* 2001, Dec, 1129-1133) as evidenced by Baumann et al. (*Physiol. Rev.* 2001. 81:871-927) and Billon et al. (*J. Cell Sci.* 2002. 115:3657-3665). This rejection is respectfully traversed.

The examiner contends that Zhang, as a secondary reference in support of the primary Gearhart reference, teaches differentiation of human ES cells toward specific cell lineages such as O4+, O1+ oligodendrocytes and refers to pages 1129-1130 in particular. However, contrary to the examiner's assertion, the only mention of O4, O1 markers at page 1129 (see top of right column) is that the flat cells at the

periphery of differentiating embryoid bodies (EBs) were immunonegative for the O4 and O1 markers. Likewise, at page 1130, it is taught near the middle of the right column that oligodendrocytes were not observed under standard culture conditions and that when cells were grown in the presence of the PDGF-A growth factor, only a few O4 immunoreactive cells with a typical multipolar oligodendroglial morphology were observed. Accordingly, one of ordinary skill in the art reading Zhang would not expect that the method of Gearhart (even if one were to accept that "neurospheres" are generated during Gearhart's process, which applicants do not concede) would lead to specifically enhancing differentiation into the O1+ and/or O4+ oligodendrocyte lineages in the face of Zhang's teaching that few if any O4+ oligodendrocytes (and certainly none of the mature O1+ oligodendrocytes) are produced.

In Gearhart, the only disclosure of a factor that can induce differentiation (of mouse ES cells) to form neuronal and glial precursors positive for the oligodendrocyte (O4) marker is at column 14, lines 59-62. Gearhart discloses at column 9, lines 4-12, that EG cells may be dependent on some growth factors for maintenance in the cultured state, one of which is bFGF and another is LIF. The only disclosure in Gearhart of other gp130 activators is at column 15, lines 57-61, where LIF and IL-6, among others, are identified as

factors that can give rise to hematopoietic progenitor cells from EG cultures. There is however no teaching whatsoever in Gearhart that gp130 activators are used in order to specifically differentiate cells (i.e., neurospheres, that may be obtainable from embryoid bodies) into O1+ and/or O4+ oligodendrocytes. In view of the teachings in Zhang, one of ordinary skill in the art would certainly have no expectation that O1+ and/or O4+ oligodendrocytes would be generated from Gearhart's method, despite Gearhart's disclosure at column 15, lines 25-35 that oligodendrocytes, along with neurons and astrocytes are expected to form. In any case, the presence of neurons and astrocytes and some oligodendrocytes (a few according to Zhang) would not satisfy the requirement in the presently claimed method that the culture medium specifically enhances differentiation into the O1+ and/or O4+ oligodendrocyte lineages, thereby causing the NS to preferentially differentiate into the O1+ and/or O4+ oligodendrocyte lineages.

The Billon and Baumann references do not fulfill the deficiencies in Gearhart and Zhang. These two references are only cited and applied by the examiner as evidence that human derived ES cells can form EBs and neurospheres in culture in the presence of FGF-2 and that the markers of differentiated oligodendrocytes include O1+ and O4+.

